Docket No.: B0877.70025US00
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant:	Jill A. O'Loughlin *et al.*
Serial No.:	10/731877
Confirmation No.:	9392
Filed:	December 9, 2003
For:	SYSTEMS AND METHODS RELATED TO DEGRADATION OF UREMIC TOXINS
Examiner:	A. M. Ford
Art Unit:	1651

DECLARATION UNDER 37 C.F.R. §1.132

I, Michael J. Lysaght, declare that:

1. I am a Professor of Medical Science and Engineering at Brown University. There, I am the Director of Biomedical Engineering at the Artificial Organs Laboratory of the Department of Molecular Pharmacology and Biotechnology. From 1987 to 1989 I was Vice-President for renal therapy research at Baxter Healthcare in Deerfield, Illinois, which was then one of the world's largest suppliers of products for the treatment of kidney failure.

2. I received an A.B. from Georgetown University, a B.S. and an M.S. in Chemical Engineering from the Massachusetts Institute of Technology, and a Ph.D. in Biomedical Engineering from the University of New South Wales.

3. I have read and understood the specification of U.S. Pat. Apl. 10/731,877 and the office action issued on January 25, 2006 (hereinafter, the "Office Action"). I have also read and understood the references cited in the Office Action, including the following references:

(a) Chang, *et al.*, "Microencapsulated genetically engineered microorganisms for clinical application," U.S. Patent No. 6,217,859, issued on April 17, 2001 (hereinafter, "Chang");

(b) Ranganathan, *et al.*, "Compositions and methods for alleviating symptoms of uremia in patients," U.S. Pat. Apl. Pub. No. 2001/0051150, published on December 13, 2001 (hereinafter, "Ranganathan");

(c) Yamamoto, *et al.*, "DNA fragment containing a gene encoding creatinine amidohydrolase," U.S. Patent No. 5,627,065, issued on May 6, 1997 (hereinafter, "Yamamoto");

(d) Shigyo, *et al.*, "Isolated recombinant uricase," U.S. Patent No. 5,728,562, issued on March 17, 1998 (hereinafter, "Shigyo"); and

(e) The Online Medical Dictionary, "Uricase," http://cancerweb.ncl.ac.uk/cgi-bin/omd, last accessed on February 28, 2005 (hereinafter "The Online Medical Dictionary").

4. I am a co-inventor of this application. I have an interest in the issuance of this application as a patent. I am employed by Brown University, and a portion of any royalties derived from licensing of the intellectual property represented by this patent application will flow to me.

5. On pages 6-9 of the Office Action, the Patent Office has rejected claims 40, 44, 45, 62, and 66 under 35 U.S.C. §103(a) as being unpatentable over Chang in view of Ranganathan, Yamamoto, and Shigyo, in light of The Online Medical Dictionary and "IUBMB Nomenclature."

6. Chang appears to be relied on in the Office Action to teach an article comprising an oral delivery composition, comprising a microencapsulated genetically engineered microorganism in a pharmaceutically acceptable carrier.

7. The Office Action states that at the time the invention was made, it was known that urea, creatinine and uric acid were all present in the small intestine of uremic patients, each in sufficient quantities that require removal for effective treatment of renal failure associated with uremia, as is taught in Ranganathan.

8. The Office Action states that it would have been obvious to one of ordinary skill in the art at the time the invention was made to additionally transfect a cell with uricase and creatininase genes so that the cell also produces uricase and creatininase, for the breakdown of uric acid and creatininase. The Office Action indicates that The Online Medical Dictionary and "IUBMB Nomenclature 'EC 3.5.2.10'" show evidence that uricase and creatininase are known to break down uric acid and creatininase, respectively.

9. I have not read the reference relied on by the Patent Office to support the statements in the Office Action regarding "IUBMB Nomenclature." The Patent Office did not supply this reference with the Office Action or in prior office actions.

10. The Office Action concludes that one of ordinary skill in the art would have been motivated to use cells transfected with each of the uricase, creatininase, and urease genes so the cell would produce uricase, creatininase, and urease for the effective breakdown of uric acid, creatinine, and urea, respectively, in a uremic patient.

11. The Office Action also notes that Chang shows that oral delivery of microorganisms expressing urease successfully decreased urea levels in uremic patients, and thus, one would

expect expression of creatininase and uricase in the gastrointestinal tract would also result in the successful decrease of creatinine and uric acid in uremic patients.

12. The Office Action further notes that it was known at the time the invention was made how to transfect microorganisms, including *E. coli*, with creatininase and uricase genes, as evidenced by Shigyo and Yamamoto.

13. I do not agree that one of ordinary skill in the art, in reading Chang and Ranganathan, would have been motivated to modify the teachings of Chang to additionally include transfecting *E. coli* with uricase and creatininase, as there would have been no reasonable expectation of success for the proposed combination.

14. Although Chang describes experiments in which empty microcapsules, devoid of bacteria, were used as controls, as well as experiments in which non-encapsulated *E. coli* were used, Chang does not describe experiments that elucidate the mechanism by which *E. coli* is able to degrade urea. Accordingly, one of ordinary skill in the art can only speculate how the urea in Chang was degraded by the genetically engineered *E. coli*.

15. It is not reasonable to assume that the mechanism (or mechanisms) by which *E. coli* is able to degrade urea in Chang will be the same mechanism by which uric acid and creatinine can be degraded in *E. coli* (assuming that degradation occurs). Uric acid and creatinine have different molecular properties than urea (e.g., physical size, molecular weight, diffusivity, etc.), and thus one cannot reasonably assume that, since *E. coli* is effective at degrading urea, *E. coli* would be equally effective at degrading uric acid and creatinine.

16. It is also not reasonable to assume that the same mechanism will operate to degrade uric acid and creatinine when the mechanism by which *E. coli* degrades urea is not known. One cannot extrapolate or predict the degradation behavior of uric acid and creatinine in *E. coli* when the mechanism of urea degradation in *E. coli* is not known. One does not know which physical parameters are the most important in order to make such an extrapolation or prediction. Without predictability, there would accordingly be no reasonable expectation of success that *E. coli* would be effective at degrading uric acid and creatinine.

17. In the alternative, the Office Action states that Chang, Shigyo, and Yamamoto teach examples where urease, uricase, and creatininase genes were respectively transfected into *E. coli* cells, and that it would have been obvious to one of ordinary skill in the art to use any suitable microorganism as the host cell in which to transfect the three genes of interest, as the choice of host microorganism would have been a matter of experimental design choice.

18. The Office Action states that one of ordinary skill in the art would have been motivated to use any suitable microorganism because Chang teaches that any suitable microorganism can be used in Chang.

19. The Office Action concludes that one of skill in the art would have expected success because one of ordinary skill in the art would be able to select a microorganism suitable for transfection and *in vivo* use as methods of transfection were well known in the art, as evidenced by Shigyo and Yamamoto, and Chang teaches methods of encapsulation of cells.

20. As described above in Paragraphs 14-16, Chang does not describe experiments to elucidate the mechanism by which *E. coli* is able to degrade urea.

21. Shigyo teaches producing isolated uricase using a cell transfected with a uricase gene, but does not teach treating uremic toxicity in a subject, for example, by administering an encapsulated cell transfected with a uricase gene.

22. Yamamoto teaches a DNA sequence comprising a creatininase gene, but does not teach treating uremic toxicity in a subject, for example, by administering an encapsulated cell transfected with a creatininase gene.

23. None of Chang, Shigyo, and Yamamoto teaches experiments that elucidate the mechanism by which *E. coli* is able to degrade urea.

24. As mentioned, it is not reasonable to assume that the mechanism (or mechanisms) by which *E. coli* is able to degrade urea in Chang will be the same mechanism by which uric acid and creatinine can be degraded in *E. coli* (assuming that degradation occurs), and thus, one cannot reasonably expect that since *E. coli* is effective at degrading urea, *E. coli* would be equally effective at degrading uric acid and creatinine.

25. As mentioned, it is also not reasonable to assume that the same mechanism will operate to degrade uric acid and creatinine when the mechanism by which *E. coli* degrades urea is not known. One cannot extrapolate or predict the degradation behavior of uric acid and creatinine in *E. coli* when the mechanism of urea degradation in *E. coli* is not known. Accordingly, there would be no reasonable expectation of success that *E. coli* would be effective at degrading uric acid and creatinine.

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26. Accordingly, one of one of ordinary skill in the art, in reading Chang, Shigyo, and Yamamoto, could not reasonably rely on these teachings to reasonably expect that the modification of the *E. coli* in Chang with Shigyo and Yamamoto would have been effective at degrading uric acid and creatinine.

27. All statements made herein of my own knowledge are true and all statements made on information and belief are believed to be true; and further, these statements were made with knowledge that willful false statements and the like are punishable by fine or imprisonment, or both, under §1001 of Title 18 of the United States Code, and that any such willful false statements may jeopardize the validity of this application or any patent issued thereon.

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23 May 2006
Date

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